85. *Experiments on the Synthesis of Purine Nucleosides. Part VI. The Synthesis of 9-d-Xylosido-2-methyladenine and of 6-d-Xylosidamino-2-methylpurine.*

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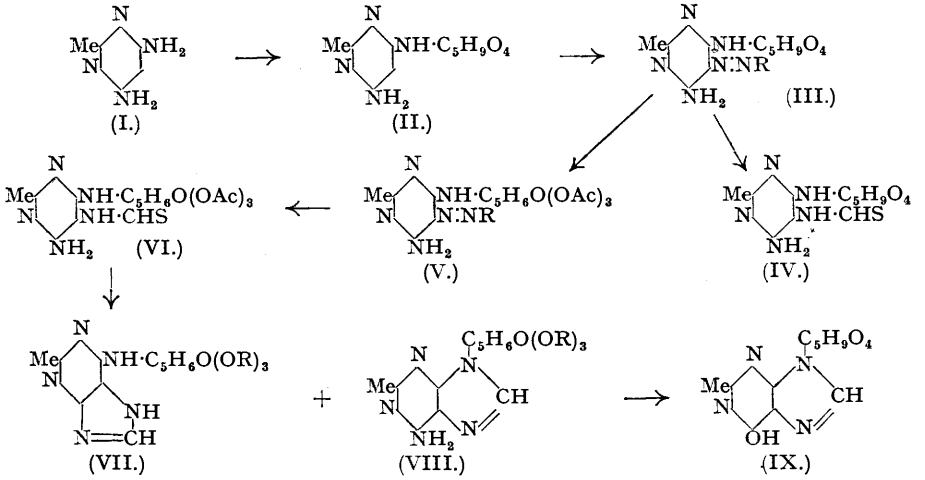
Application of the experience gained in model experiments described in earlier papers of this series to the synthesis of purine nucleosides has now led to the total synthesis of 9-d-*xylosido*-2-*methyladenine* and of 6-d-*xylosidamino*-2-*methylpurine*. The former is readily deaminated to 9-d-*xylosido*-2-*methylhypoxanthine* but the latter cannot be deaminated. The ultra-violet absorption of the two synthetic xylosides of 2-methyladenine has been measured and compared with the corresponding data for the sugar-free purine and for 2 : 7-*dimethyladenine* and 2 : 9-*dimethyladenine*. In the course of the work, a variety of new purine and pyrimidine derivatives have been prepared.

In earlier papers of this series (J., 1943, 383, 386, 571, 574, and preceding paper) a hypothetical route to the synthesis of purine nucleosides has been examined in model experiments designed to establish the methods to be employed in the various stages. Application of the experience so gained to the total synthesis of purine glycosides forms the subject of the present communication. The synthetic method is indicated schematically below.



Condensation of 4 : 6-diamino-2-methylpyrimidine (I) with *d*-xylose under the conditions described in Part III (J., 1943, 571) gave 6-amino-4-*d*-xylosidamino-2-methylpyrimidine (II) in good yield. Our original intention was to convert this xyloside into 6-*amino*-5-*thioformamido*-4-d-*xylosidamino*-2-*methylpyrimidine* (IV) by nitrosation followed by reduction and thioformylation. This procedure has been successfully applied to glycosides analogous to (II) in which the methyl group in position 2 is replaced by a methylthio-group and will be described in a later communication. It could not, however, be applied in the case of (II) itself, since nitrosation of 4 : 6-diamino-2-methylpyrimidine and its derivatives can only be effected in presence of mineral acids which cause hydrolysis of glycosidic linkages. A suitable alternative was found in the application of the coupling of pyrimidines with diazonium compounds described in Part V (preceding paper). When (II) was coupled in sodium hydrogen carbonate solution with diazotised *p*-nitroaniline 6-*amino*-4-d-*xylosidamino*-5-*p*-*nitrobenzeneazo*-2-*methylpyrimidine* (III; R = $C_6H_4{\cdot}NO_2$) separated in good yield; unfortunately, when hydrogenated in presence of Raney nickel, the azo-compound gave a mixture of the corresponding 5-aminopyrimidine and *p*-phenylenediamine which could not easily be separated. This difficulty was surmounted by using 2 : 4-dichloroaniline in place of *p*-nitroaniline in the coupling. 6-*Amino*-4-d-*xylosidamino*-5-(2′ : 4′-*dichlorobenzeneazo*)-2-*methylpyrimidine* (III; R = $C_6H_3Cl_2$) was reduced smoothly, and the aminopyrimidine formed was converted directly and without isolation into the thioformamido-compound (IV). In this instance it was found more convenient to carry out the thioformylation by shaking the amine solution with dithioformic acid than by our common procedure of allowing the amine to react with aqueous sodium dithioformate.

Attempts to convert (IV) into a xylosido-purine by refluxing in pyridine solution were made, but the yield of purine seemed very small and extensive decomposition occurred during the operation. It was thought that decomposition might be considerably reduced if the sugar hydroxyls in (IV) were acetylated before ring closure was carried out. Direct acetylation of (IV) did not readily yield a homogeneous product, but the desired object was achieved in a slightly different way. When the azo-compound (III; R = $C_6H_3Cl_2$) was acetylated in the cold with acetic anhydride–pyridine, 6-*amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 4′-*dichlorobenzeneazo*)-2-*methylpyrimidine* (V; R = $C_6H_3Cl_2$) was formed. Hydrogenation of this acetate, followed by treatment of the reduced product with dithioformic acid, gave 6-*amino*-5-*thioformamido*-4-*triacetyl*-d-*xylosidamino*-2-*methylpyrimidine* (VI) in satisfactory yield.

The acetyl derivative (VI) was readily soluble in pyridine, and on boiling the solution hydrogen sulphide

was freely evolved. When gas evolution ceased the pyridine was removed and the residue triturated with ethyl acetate. A portion of the material dissolved, leaving a crystalline mass of 6-*triacetyl*-d-*xylosidamino*-2-*methylpurine* (VII; R = Ac), which had been formed by ring-closure between the 5-thioformamido-group of (VI) and the 6-amino-group. On treatment with methanolic sodium methoxide, this product underwent deacetylation, giving 6-d-*xylosidamino*-2-*methylpurine* (VII; R = H). Evaporation of the ethyl acetate mother-liquors left after removal of (VII; R = Ac) gave a resinous acetylated xyloside which on deacetylation yielded the desired 9-d-*xylosido*-2-*methyladenine* (VIII; R = H) in crystalline condition. Proof of the correctness of the structures (VII) and (VIII) allotted to these products was obtained in the following way.

The xyloside (VII; R = H) is hydrolysed very readily by 0·1N-mineral acids to 2-methyladenine and *d*-xylose. Hydrolysis under such mild conditions is a normal property of 4- or 6-glycosidaminopyrimidines, whereas hydrolysis of (VIII; R = H) or of the synthetic adenine *d*-glucoside of Fischer and Helferich (*Ber.*, 1914, **47**, 210), which is believed to be a 9-*d*-glucoside (Gulland and Story, J., 1938, 259), is much more difficult. Moreover, (VII; R = H) is readily soluble in alkali. Alkali solubility is a property of adenine or 2-methyladenine derivatives bearing no substituent on an imidazole nitrogen; it is absent in, *e.g.*, 2 : 7-*dimethyladenine* and 2 : 9-*dimethyladenine*. That the xylose residue is present in a 6-xylosidamino-group is also shown by the fact that (VII; R = H) cannot be deaminated with nitrous acid whereas its hydrolysis product, 2-methyladenine, on similar treatment readily yields 2-*methylhypoxanthine*. Incidentally, this failure to deaminate (VII; R = H) before hydrolysis of the glycosidic linkage can be regarded as additional proof of the structure of the pyrimidine xyloside (II); clearly, had the sugar residue in (II) been attached to one of the nuclear nitrogen atoms deamination of any purine glycoside prepared from it would have been readily accomplished.

2 : 7- and 2 : 9-Dimethyladenine which were required for purposes of comparison with the synthetic xylosides were formed simultaneously on methylating 2-methyladenine with methyl iodide in methanolic sodium methoxide. This method of methylating purines is commonly regarded as giving rise to the 9-substituted derivative (Krüger, *Z. physiol. Chem.*, 1894, **18**, 434), but it seems likely that the production of both 7- and 9-methyl derivatives by this method is fairly general. As both our products were insoluble in alkali, it followed that methylation must in each case have occurred on an imidazole nitrogen; hence, proof of structure of the substance described as 2 : 9-dimethyladenine would automatically fix the other as 2 : 7-dimethyladenine. This proof was obtained by direct synthesis. 6-*Amino*-4-*methylamino*-2-*methylpyrimidine* was coupled with diazotised *p*-chloroaniline and the *azo-compound* formed was hydrogenated. The 5-amino-compound produced was not isolated but converted directly into 6-*amino*-5-*thioformamido*-4-*methylamino*-2-*methylpyrimidine* which was cyclised by heating in quinoline to 2 : 9-dimethyladenine (cf. Part I; *loc. cit.*). That the cyclisation had proceeded in the desired direction was shown, not only by the alkali-insolubility of the product, but also by its ready deamination to 2 : 9-*dimethylhypoxanthine*.

The xyloside (VIII; R = H) is insoluble in alkali and is hydrolysed by N-sulphuric acid to 2-methyladenine and *d*-xylose. On treatment with nitrous acid it is deaminated, giving 9-d-*xylosidamino*-2-*methylhypoxanthine* (IX). There can therefore be no doubt but that it is 9-*d*-xylosido-2-methyladenine, since the method of synthesis excludes the possibility of the xylose residue being in position 7. The simultaneous production of (VII; R = Ac) and (VIII; R = Ac) on cyclisation of (VI) was unexpected in view of the exclusive formation of the 9-methylpurine on cyclising 6-amino-4-methylamino-5-thioformamido-2-methylthiopyrimidine (Part I; J., 1943, 383) and of some preliminary experiments on other analogous acetyl-free glycosides. Until further studies have been made no complete explanation can be offered.

The work described represents the first instance of the synthesis of purine glycosides by methods establishing their constitution. The synthesis of (VIII; R = H) has an added interest since by a similar route 9-*d*-ribosidoadenines should be accessible, including the important natural nucleoside adenosine (9-*d*-ribofuranosidoadenine). Experiments on the synthesis of adenosine are in progress and will be reported in due course.

Bearing in mind the extension of the synthetic method to adenosine, it is important to determine whether the glycosides described in this paper have a furanose or a pyranose structure. Experiments now in progress will, it is hoped, clarify this aspect of structure for all our synthetic glycosides. Meanwhile it may be noted that we failed to obtain any evidence of tritylation on treating (II) with trityl chloride under the usual conditions. This result is by no means conclusive, since the low solubility of the xyloside would probably militate against tritylation in any case. Again, it would seem from a comparison of literature references to the hydrolysis of adenosine with those dealing with the hydrolysis of the 9-*d*-glucopyranosidopurines of Fischer and Helferich (*loc. cit.*), that hydrolysis of furanosides is much the more easily effected. 9-*d*-Xylosido-2-methyladenine is recovered unchanged after treatment with dilute acid of a strength known to hydrolyse adenosine, but it does hydrolyse with stronger acid under precisely the same conditions as the glucosides of Fischer and Helferich. These facts would make it appear probable that all the xylosides described in this paper are pyranosides. It must, of course, be admitted that, since the configuration of the natural nucleosides or the synthetic glycosides has not been determined, it is possible that the differences in ease of hydrolysis might be due merely to a difference between α- and β-glycosides.

It may be recalled that the only evidence adduced in support of the 9-glycosidic structure of the natural purine nucleosides is that of Gulland *et al.* (J., 1934, 1639; 1936, 765; 1937, 1912; 1938, 259, 692), who showed that the natural compounds resembled in their ultra-violet absorption 9-alkyl- rather than 7-alkyl-purines. Dr. A. E. Gillam has made corresponding absorption-spectrum measurements both of our synthetic xylosides and of sugar-free 2-methyladenine derivatives. The results are shown in the Table.

	N/10-HCl.		N/10-NaOH.	
	$\lambda_{max.}$	ϵ.	$\lambda_{max.}$	ϵ.
2-Methyladenine	2655	12,900	2710	10,700
2 : 7-Dimethyladenine	2730	16,200	2770	13,200
2 : 9-Dimethyladenine	2640	12,700	2640	16,200
9-*d*-Xylosido-2-methyladenine	2605	12,500	2625	14,700
6-*d*-Xylosidamino-2-methylpurine	2755	17,000	2745	14,300

Detailed interpretation of absorption-spectrum measurements in such complex molecules is difficult in the absence of further data, and we would hesitate to draw any far-reaching conclusions on comparatively minor differences, especially when it is remembered that the absorption spectrum of adenine is very much influenced by the pH of the solution in which it is measured (Loofbourow and Stimson, J., 1940, 845). Nevertheless, the location of the absorption maximum in the synthetic 9-xylosido-2-methyladenine is much closer to that of 2 : 9-dimethyladenine than to that of 2 : 7-dimethyladenine. In this sense the results recorded in the table would support the conclusions drawn by Gulland and his collaborators.

Experimental.

6-*Amino*-4-d-*xylosidamino*-5-p-*nitrobenzeneazo*-2-*methylpyrimidine* (III; R = $C_6H_4{\cdot}NO_2$).—*p*-Nitroaniline (0·26 g.), dissolved in water (10 c.c.) and hydrochloric acid (1·52 c.c., *d* 1·16), was diazotised at 0° by adding sodium nitrite (0·14 g. in 10 c.c. of water). The diazo-solution was added rapidly to a freshly prepared solution of 6-amino-4-*d*-xylosidamino-2-methylpyrimidine (0·52 g.; Part III, *loc. cit.*) in water (20 c.c.) containing 3 drops of concentrated hydrochloric acid. The resulting solution was poured into sodium hydrogen carbonate (1·6 g.) in water (100 c.c.), and the mixture left for 2 hours. The *azo-glycoside* was collected. Recrystallised from pyridine–aqueous alcohol, it formed small, red plates, m. p. 230° (decomp.); it gave a positive Molisch reaction (Found: C, 47·0; H, 4·9; N, 24·6. $C_{16}H_{19}O_6N_7$ requires C, 47·4; H, 4·7; N, 24·2%). The azo-glycoside (0·2 g.) was recovered unchanged after 2 hours' heating at 90° with trityl chloride (0·4 g.) in pyridine (10 c.c.).

6-*Amino*-4-d-*xylosidamino*-5-(2′ : 4′-*dichlorobenzeneazo*)-2-*methylpyrimidine* (III; R = $C_6H_3Cl_2$).—2 : 4-Dichloroaniline (2·7 g.), dissolved in water (150 c.c.) containing hydrochloric acid (6·5 c.c., *d* 1·16), was diazotised by adding sodium nitrite (1·2 g. in 10 c.c. of water), and the solution added to a suspension of 6-amino-4-*d*-xylosidamino-2-methylpyrimidine (5·0 g.) in water (100 c.c.). The resulting clear solution was poured into aqueous sodium hydrogen carbonate (13 g. in 200 c.c.). The *azo-compound* soon began to separate, and after 1½ hours it was collected, washed with water, and dried in a desiccator over calcium chloride. It was recrystallised by dissolving it in a minimum of hot pyridine, adding hot alcohol (3 vols.), filtering, and cooling to 0°; it formed small yellow plates, m. p. 218—219° (decomp.), which gave a positive Molisch reaction (Found, in material dried at room temp.: C, 41·0; H, 4·8; N, 17·6; loss at 120° in a high vacuum over P_2O_5, 9·7. $C_{16}H_{18}O_4N_6Cl_2,2\frac{1}{2}H_2O$ requires C, 40·6; H, 4·9; N, 17·7; loss on drying, 9·5%). The yield was almost quantitative.

6-*Amino*-5-*thioformamido*-4-d-*xylosidamino*-2-*methylpyrimidine* (IV).—The foregoing pyrimidine (2 g.) was hydrogenated in alcoholic solution at 70° under 120 atm. for 7 hours in presence of Raney nickel. The colourless solution obtained after filtering off the catalyst was evaporated to dryness in a vacuum, the residue triturated with a little water, and 2 : 4-dichloroaniline removed by extraction with ether. Sodium dithioformate (0·75 g. in 2 c.c. of water) was added to the aqueous layer, and after standing under nitrogen for several days, the solution was concentrated in a vacuum until the *thioformyl* derivative crystallised. The product was collected, and recrystallised from aqueous alcohol; colourless needles, m. p. 232° (decomp.) (Found, in sample dried at room temp.: C, 40·1; H, 6·2; N, 21·0; loss at 80° in a high vacuum over P_2O_5, 6·0. $C_{11}H_{17}O_4N_5S,H_2O$ requires C, 39·8; H, 5·7; N, 21·1; loss on drying, 5·4%). The yield by this method was variable (maximum 50%). The following is a better method of preparation.

The alcoholic solution obtained after reduction of the azo-compound is evaporated in a vacuum to a small volume, and ether (150 c.c.) added to precipitate the amorphous glycoside, which is collected, washed with ether, and dissolved in water (50 c.c.); dithioformic acid (2 g.) is then added. The mixture is shaken overnight, a further 2 g. of dithioformic acid added, and shaking continued for a further 12 hours. The mixture is now warmed to 50° and filtered, the filter residue being washed with water. On evaporating the combined filtrate and washings in a vacuum to small bulk and adding alcohol, the thioformyl derivative crystallises out in almost pure condition (yield, 50%).

6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 4′-*dichlorobenzeneazo*)-2-*methylpyrimidine* (V; R = $C_6H_3Cl_2$).—The azo-compound (III; R = $C_6H_3Cl_2$) (1 g.) was dissolved in dry pyridine, acetic anhydride (2 c.c.) added to the cooled solution, and the mixture kept overnight. After addition of absolute alcohol (10 c.c.) and leaving for 1 hour, the solvents were removed in a vacuum, the residue evaporated once more with a small amount of absolute alcohol, and recrystallised from benzene or from pyridine–alcohol. The product formed small yellow plates with a rather indefinite decomposition point at 230° (Found, in material dried at 100°: C, 46·0; H, 4·5; N, 14·8. $C_{22}H_{24}O_7N_6Cl_2$ requires C, 45·7; H, 4·2; N, 14·6%); yield, 90%.

6-*Amino*-5-*thioformamido*-4-*triacetyl*-d-*xylosidamino*-2-*methylpyrimidine* (VI).—The above acetylated azo-glycoside (V; R = $C_6H_3Cl_2$) (2 g.), suspended in ethyl acetate, was hydrogenated in presence of Raney nickel at 70° under 100 atm. during 8 hours. The filtered solution was evaporated in a vacuum to small bulk, and light petroleum (100 c.c., b. p. 40—60°) added. The amorphous precipitate was collected, dissolved in benzene (50 c.c.), and shaken for 48 hours with dithioformic acid (3 g. added initially and a further 3 g. after 24 hours). The mixture was now filtered, the solid residue being washed with hot benzene. Filtrate and washings were combined, evaporated in a vacuum, and the residue dissolved in a minimum of ethyl acetate and set aside. The *thioformyl* derivative which slowly separated was recrystallised from a mixture of alcohol, ethyl acetate, and light petroleum; colourless needles, m. p. 148° with evolution of gas (Found, in material dried at 70°: C, 45·8; H, 5·3; N, 15·3. $C_{17}H_{23}O_7N_5S$ requires C, 46·0; H, 5·2; N, 15·8%); yield, 75%.

Cyclisation of Thioformamido-compound (VI).—The above thioformamido-compound (3 g.) was refluxed in anhydrous pyridine (10 c.c.) in a slow stream of nitrogen for 15 hours, by which time evolution of hydrogen sulphide had ceased. The pyridine was removed in a vacuum, and the residue triturated with ethyl acetate (3 c.c.), whereupon a portion dissolved, leaving a mass of crystals.

(*a*) The above crystalline material, recrystallised from alcohol, gave 6-*triacetyl*-d-*xylosidamino*-2-*methylpurine* (VII; R = Ac) as rosettes of needles, m. p. 204—205°, containing pyridine of crystallisation (Found: C, 53·5; H, 5·7; N, 17·3. $C_{17}H_{21}O_7N_5,C_5H_5N$ requires C, 54·0; H, 5·4; N, 17·3%); yield, 15%.

(*b*) The ethyl acetate solution was evaporated to dryness. As the resinous residue did not crystallise, it was deacetylated by keeping it at room temperature with methanolic ammonia (70 c.c.) for 4 days. The mixture was now evaporated to dryness, and the residue washed with a little absolute alcohol. Recrystallisation from water gave 9-d-

xylosido-2-methyladenine (VIII; R = H) as silky needles, m. p. 288° (decomp.) (Found, in material dried at 140°: C, 47·2; H, 5·3; N, 24·6. $C_{11}H_{15}O_4N_5$ requires C, 47·0; H, 5·3; N, 24·9%); yield, 30%. The product was sparingly soluble in cold water, readily in hot. Its solubility was not increased by addition of sodium hydroxide. It had $[\alpha]_D^{19·5°}$ = − 26° (in water; *c*, 0·3).

Hydrolysis. The above xyloside (100 mg.) was recovered substantially unchanged after refluxing for 1½ hours with 0·1N-sulphuric acid. A second portion (100 mg.) was refluxed for 6 hours with N-sulphuric acid (10 c.c.). The hydrolysis solution was neutralised with sodium hydroxide and evaporated to small bulk, whereupon tiny plates (50 mg.) with the properties of 2-methyladenine separated (Found, in material dried at 140°: C, 48·1; H, 4·6; N, 47·3. Calc. for $C_6H_7N_5$: C, 48·4; H, 4·7; N, 47·0%). The filtrate, after removal of 2-methyladenine, was evaporated cautiously to dryness, the residue extracted thrice with boiling alcohol, and the combined extracts evaporated on the steam-bath. The semi-crystalline product was heated at 100° for 30 mins. with acetic anhydride (2 c.c.) and sodium acetate (20 mg.). Removal of acetic anhydride in a vacuum, followed by crystallisation of the residue from hot water, gave β-tetra-acetyl *d*-xylose (50 mg.), m. p. 126°, undepressed in admixture with an authentic specimen (m. p. 126°).

6-d-*Xylosidamino-2-methylpurine* (VII; R = H).—6-Triacetyl-*d*-xylosidamino-2-methylpurine (VII; R = Ac) (0·3 g.) was dissolved in chloroform (20 c.c.), and methanolic sodium methoxide (sodium, 0·034 g.; methanol, 20 c.c.) added. After 3 hours the solution was extracted with three successive portions of water (20 c.c.), the combined extracts neutralised to phenolphthalein with 10% acetic acid, and evaporated to dryness in a vacuum. Absolute alcohol (10 c.c.) was added, and the solid collected and recrystallised from water; long, colourless needles, m. p. 218° (decomp.) (Found, in material dried at 140°: C, 46·4; H, 5·4; N, 24·2. $C_{11}H_{15}O_4N_5$ requires C, 47·0; H, 5·3; N, 24·9%); yield, 65%. The product had $[\alpha]_D^{19°}$ = − 32° (in water; *c*, 0·3); it was sparingly soluble in cold water but readily so in dilute sodium hydroxide. It could not be deaminated by means of nitrous acid in dilute acetic acid solution at room temperature or at 60°.

Hydrolysis. The xyloside (0·12 g.) was refluxed for 1½ hours with 0·1N-sulphuric acid (10 c.c.), and the solution neutralised with sodium hydroxide and concentrated to *ca.* 2 c.c. Tiny plates (50 mg.) of 2-methyladenine separated (Found in material dried at 140°: C, 48·1; H, 4·3; N, 47·5. Calc. for $C_6H_7N_5$: C, 48·4; H, 4·7; N, 47·0%). The filtrate from the 2-methyladenine was evaporated, the residue extracted three times with boiling alcohol, and the combined extracts again evaporated. Acetylation of the residue with acetic anhydride (2 c.c.) and sodium acetate (50 mg.) at 100° and recrystallisation of the product from water gave β-tetra-acetyl *d*-xylose (50 mg.), m. p. 126°, undepressed in admixture with an authentic specimen (m. p. 126°).

Deamination of 9-d-*Xylosido-2-methyladenine.*—(a) The xyloside (VIII; R = H) (0·2 g.) was dissolved in water (10 c.c.) at 70°, barium nitrite (0·42 g.) added, and the solution cooled rapidly to 20° before addition of acetic acid (0·3 c.c.). The solution was left at room temperature for 3 days with occasional shaking, evaporated to small volume, and filtered from some barium nitrate which separated. The filtrate was made just acid to Congo-red with sulphuric acid, precipitated barium sulphate removed, and the solution evaporated to small bulk. On standing, 9-d-*xylosido-2-methylhypoxanthine* (IX) separated as small plates (0·06 g.), m. p. 203°, readily soluble in dilute sodium hydroxide (Found, in material dried for 1 hour at 100°: C, 44·1; H, 5·2; N, 18·1; loss at 140° in a high vacuum over P_2O_5, 6·2. $C_{11}H_{14}O_5N_4,H_2O$ requires C, 44·0; H, 5·3; N, 18·6; loss on drying, 6·0%).

(b) The xyloside (0·3 g.) was dissolved in warm water (10 c.c.), sodium nitrite (0·6 g.) and acetic acid (0·9 c.c.) added, and the solution maintained at 60° for 15 mins., then evaporated to small bulk. On addition of sodium hydroxide to faint alkalinity to brilliant-yellow and keeping, 9-*d*-xylosido-2-methylhypoxanthine, m. p. 203°, crystallised out (yield, 50%).

2-*Methylhypoxanthine.*—2-Methyladenine (1 g.) was dissolved in boiling water (150 c.c.) containing acetic acid (7 c.c.), the solution cooled to 60—65°, and barium nitrite (7 g.) added. The mixture was maintained at this temperature for 45 minutes, and left overnight at room temperature. A slight excess of ammonia was now added, and the solution evaporated to small bulk. 2-*Methylhypoxanthine* separated as fine needles, and was recrystallised from water; it had no m. p. below 360° (Found, in material dried at 140°: C, 47·6; H, 3·6; N, 36·7. $C_6H_6ON_4$ requires C, 48·0; H, 4·0; N, 37·4%). The same product was also obtained by ring closure of 4-amino-5-thioformamido-6-hydroxy-2-methylpyrimidine by heating in quinoline solution.

Methylation of 2-*Methyladenine.*—2-Methyladenine (1 g.) was dissolved in methanolic sodium methoxide (0·155 g. of sodium in 10 c.c. of methanol), and methyl iodide (3 g.) added. The solution was set aside for 6 days, and the crystalline solid which had separated was filtered off. Recrystallisation from water gave 2 : 7-*dimethyladenine* (0·3 g.) as colourless needles, m. p. 338° (decomp.), whose sparing solubility in cold water was not increased by addition of sodium hydroxide (Found, in material dried at 140°: C, 51·5; H, 5·8; N, 42·6. $C_7H_9N_5$ requires C, 51·5; H, 5·5; N, 43·0%).

The mother-liquors remaining after the separation of 2 : 7-dimethyladenine on concentration deposited colourless needles (0·2 g.) of 2 : 9-*dimethyladenine*, m. p. 238° (Found, in material dried at 140°: C, 51·4; H, 5·7; N, 42·8%). Its sparing solubility in cold water was not increased by addition of sodium hydroxide. A mixed m. p. with a specimen of 2 : 9-dimethyladenine synthesised by the route described below showed no depression.

6-*Amino-4-methylamino-2-methylpyrimidine.*—4-Chloro-6-amino-2-methylpyrimidine (30 g.; Part I, *loc. cit.*) was heated in an autoclave at 150° for 4 hours with aqueous methylamine (150 c.c. of 33%). The *product* which separated on cooling was recrystallised from hot water; colourless needles, m. p. 239—240° (Found, in material dried at 140°: C, 52·1; H, 7·2; N, 40·0. $C_6H_{10}N_4$ requires C, 52·2; H, 7·2; N, 40·6%). The yield was almost quantitative.

6-*Amino-4-methylamino-5-p-chlorobenzeneazo-2-methylpyrimidine.*—The foregoing pyrimidine (45 g.) was added to a solution of diazotised *p*-chloroaniline (from 43 g. of base in 250 c.c. of 13% hydrochloric acid), and the mixture poured into slight excess of aqueous sodium hydroxide (10%). The yellow *azo-compound* which was precipitated was collected, washed, and recrystallised from pyridine; yellow plates, m. p. 207° (decomp.) (Found, in material dried at 140°: C, 52·3; H, 4·8; N, 30·3. $C_{12}H_{13}N_6Cl$ requires C, 52·1; H, 4·7; N, 30·4%); yield, 75%.

6-*Amino-5-thioformamido-4-methylamino-2-methylpyrimidine.*—The above azo-compound (30 g.) was suspended in alcohol (400 c.c.) and hydrogenated at 110° for 4 hours under 100 atm., a Raney nickel catalyst being used. The pale brownish solution was filtered, evaporated to dryness in a vacuum, and water (250 c.c.) added. After removal of *p*-chloroaniline by ether extraction, sodium dithioformate (45 g.) was added, and the filtered aqueous solution left overnight. The *thioformamido*-compound which separated was collected and recrystallised from water; colourless, slender plates, m. p. 189° with gas evolution (Found, in material dried at room temperature: C, 43·1; H, 5·9; N, 35·5. $C_7H_{11}N_5S$ requires C, 42·7; H, 5·6; N, 35·6%). The yield was almost quantitative.

2 : 9-*Dimethyladenine.*—The above thioformamido-compound (5 g.) was refluxed in quinoline (25 c.c.) for 5 mins., and the solution cooled and diluted with ether. The 2 : 9-dimethyladenine which separated was recrystallised from water, forming long needles, m. p. 238°, undepressed in admixture with a specimen prepared by methylating 2-methyladenine (above); yield, 92%.

Additional proof that the product is indeed 2 : 9-dimethyladenine was obtained in the following way. The material (1 g.) was dissolved in water (20 c.c.) containing acetic acid (5 c.c.) at 65°, sodium nitrite (4 g.) added, and the solution maintained at 60—65° for 1 hour. The solution was now neutralised to phenolphthalein with sodium hydroxide and

evaporated to small bulk. On cooling, 2 : 9-*dimethylhypoxanthine* separated; recrystallised from water, it formed colourless needles, which on heating appeared to decompose at *ca.* 330° (Found, in material dried at 140° : C, 51·8; H, 5·0; N, 34·4. $C_7H_8ON_4$ requires C, 51·2; H, 4·9; N, 34·2%); yield, 90%.

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